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Original Research Article

A Prospective, Open Label, Randomized Control Trial to Evaluate the Efficacy, Changes in Quality of Life and Treatment Adherence of Oral Rosuvastatin in Management of Plaque Psoriasis

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Abstract

Background: Psoriasis is a chronic, autoimmune, inflammatory disease characterized by scaly red patches on the skin that has great negative effect on quality of life. Rosuvastatin, a lipid-lowering medication, is considered a promising drug in treating plaque psoriasis due to their pleiotropic effect.

Objectives: To evaluate efficacy of oral rosuvastatin with escalating doses on mild to moderate plaque psoriasis with Psoriasis Area and Severity Index (PASI), to assess the effectiveness of rosuvastatin in improving quality of life using Dermatology Life Quality Index (DLQI), and to assess medication adherence using Medication Adherence Rating Scale (MARS).

Methods: An open label, randomized control trial, where 52 patients with plaque psoriasis were enrolled after considering inclusion and exclusion criteria. Patients were randomly divided into four groups: a control group that received standard therapy consisting of topical glucocorticoids, antihistaminic and skin emollient and treatment groups receiving 5mg,10mg, 20 mg of rosuvastatin along with standard treatment continued daily for 8 weeks. Patients were assessed for PASI, DLQI scores, routine blood parameters and LFT tests done at baseline,4 weeks and 8 weeks, while MARS was assessed at 4 weeks and 8 weeks. Results were statistically analysed using GraphPad Prism version 9 software. For intragroup comparison at 0, 4 and 8 weeks, repeated measures ANOVA was done. Intergroup comparisons were done by one-way ANOVA and statistical significance implied by p value<0.05.

Results: At the end of the study, while on intragroup comparison all the groups showed significant improvement in PASI (p<0.0001), DLQI (p<0.0001) and MARS score (p<0.0001) at 4 weeks and 8 weeks, on intergroup comparison, none of the intervention groups had any significant advantage over the control group in terms of change of PASI, DLQI or MARS across the study duration. There was also a significant rise in hepatic ALT (p<0.001) and AST (p<0.001) enzymes levels in all the rosuvastatin receiving groups while the control group had a reduction in the ALT levels (p = 0.0012).

Conclusion: Oral rosuvastatin in any of the clinically given doses of 5 mg, 10 mg or 20 mg failed to provide any extra benefits when added to the standard treatment of topical glucocorticoids, antihistaminic and skin emollient cream.

Keywords: Plaque psoriasis, Rosuvastatin, anti-inflammatory, PASI, DLQI, MARS.

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Introduction

Psoriasis is a chronic, noncommunicable, immune mediated inflammatory disease. It primarily involves the skin associated with multifactorial disorder characterized hyperproliferative by keratinocyte and infiltration of lymphocytes, dendritic cell, macrophages, and neutrophils leading to the development of thick, scaly plaques on the skin, that has great negative impact on patient's quality of life (QoL) [1].

Plaque psoriasis is one of the most common clinical types of psoriasis. Although the condition is not life threatening, it is difficult to treat, and response rates vary widely [2]. The most common form of psoriasis is Psoriasis vulgaris, seen in 90% of patients. It appears as red, scaly, symmetrically distributed plaques localized to the extensor aspects of the extremities, particularly the elbows and joints, and with scalp, lower lumbosacral, buttocks, and genital involvement [3]. According to a study reported in 2017 in the Anais Brasileiros de Dermatologia, people with psoriasis are six times more likely to have metabolic syndrome, this in comparison to others without psoriasis [4]. Psoriasis is also associated with painful, disfiguring and disabling joints, and few other conditions, including osteoporosis, uveitis, and liver and kidney disease. Inflammatory conditions are known for causing damage to the kidneys or liver, either directly or through whole-body inflammation that eventually leads to organ damage [5].

Though the precise pathogenesis of psoriasis in affected individual is not fully understood, but it is believed that a complex involvement between genetic,

immunological, and environmental factors may play a role. Dyslipidaemia [6] and elevated levels of pro-inflammatory cytokines [7] play a significant role in the development and progression of psoriasis. Results from genome wide scan in 2009 revealed that HLA-C, genes involved in IL-23 and NF-kappa B signalling (TNIP1, TNFAIP3) and modulation of Th2 immune responses (IL4, IL13) are associated with pathogenesis of psoriasis [8]. Obesity is also associated to systemic inflammation because of the release of adipokines, including chemerin, adiponectin, resistin, visfatin, C-reactive protein released by macrophages, and T cells infiltrating visceral adipose tissue [9,10]. Adipokines can contribute to the pathogenesis of insulin resistance and promote inflammation associated with psoriasis [11,12]. isoprenoids particular, the farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) that play vital role in regulation of lipid synthesis are also essential for the post-translational modification of small guanosine triphosphate (GTP)-binding proteins or GTPases, such as members of the Ras, Rho, and Rab families [13]. Several studies demonstrated the importance of GTPases in various cell signalling pathways by their action as molecular switches, including those that regulate cell growth, proliferation, and inflammation [14].

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The various modalities of treating psoriasis comprise common first line treatments like phototherapy, topical therapies (such as corticosteroids, vitamin D analogues), or systemic medications and an array of biologic agents. These therapies have

limitations due to the lack of long-term efficacy and safety data [15].

HMG-CoA reductase inhibitors (statins) has gained considerable interest in greater number of psoriasis patients due to pleotropic effects, beyond its lipid lowering action. Such pleiotropic effects include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects anti-inflammatory properties, and stabilization atherosclerotic plaques [16]. Moreover, in the skin, statins favour Th1-mediated immune responses and inhibit the induction of MHC II, prevent cytokine release from mast cells and mast cell degranulation, and interactions between inflammatory chemokines [17,18]. Though treatment of psoriasis is mainly based on controlling the symptoms, statins due to its pleotropic effects, reduce inflammatory markers that in theory has the potential to be useful in inflammatory disorder like However, psoriasis. few studies [19,20,21,22] that have examined the effectiveness of the different statins in psoriasis have produced conflicting reports, necessitating further research on this topic.

Rosuvastatin is a commonly used high potency and high efficacy HMG-CoA reductase inhibitor. Its unique advantages include high hydrophilicity that increases uptake via hepatic organic transporting polypeptide-1B1 (OATP-1B1) and thereby ensures high bioavailability at the target of action; while peripheral distribution is less significant, that greatly contributes to its safety [23]. It also has high affinity for the target HMG-CoA reductase enzyme leading to slow enzyme recovery and a longer duration of action compared to the other statins [24]. All these factors have established rosuvastatin as one of the most popular statins used in clinical practice, and it is commonly prescribed in doses of 5 mg, 10 mg, and 20 mg [25].

While rosuvastatin has potent lipidlowering actions, as pleotropic effects are a class action of statins, rosuvastatin has potential to be effective in psoriasis. In the (ROsuvastatin RORA-AS study Rheumatoid Arthritis. Ankylosing Spondylitis and other inflammatory joint diseases), rosuvastatin was shown to improve atherosclerosis. including regression of atherosclerotic plaques, reduction of carotid wall stiffness, and improved endothelial function [26]. However. there are very limited observations that have analysed the effects of different doses of rosuvastatin in treatment of psoriasis.

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To measure the severity and extent of psoriasis, Psoriasis Area and Severity Index (PASI) is a widely popular and reliable index that takes into account erythema, induration, and scaling in four broad regions of body and produces a composite score that can be easily analysed and compared [27,28].

However, PASI does not consider the effect of the disease on the quality of life and psychological wellbeing of the patients of psoriasis; and patient's interpretation of quality of life can be often worse than clinical severity of the disease [29]. To address this issue, Dermatology Life Quality Index or DLQI is the most frequently used patient reported outcome measure in dermatology practise that provides a good measure of the patient's perception of their quality of life in context of the treatment [30,31].

It is important to consider that adherence to the prescribed medication is a crucial determinant of treatment success. Nonadherence has been observed in alarming proportions in management of chronic diseases and leads to poor health outcome and increased cost of therapy. Assessment of treatment adherence particularly in context of chronic disease like psoriasis can give valuable insights regarding patients attitudes and compliance towards the treatment regimen and can influence the effectiveness of the therapy

[32]. The Medication Adherence Report Scale (MARS) is a simple questionnaire that examines medication-taking behaviours and attitudes of the patient with high validity and reliability [33].

Though rosuvastatin has demonstrated reasonable safety in clinical scenarios, some significant adverse effects of the drug include severe myopathy, elevated hepatic enzymes like AST, ALT; elevated Creatinine kinase (greater than ten times the upper limit of normal), rhabdomyolysis and renal failure. In this context, a periodic measurement of liver AST and ALT enzymes is a good indicator of the safety of the drug [34].

While there is already a dearth of studies that have analysed the effects of rosuvastatin in psoriasis using instruments like PASI, DLQI or MARS, there is a particular scarcity of such observations in Indian population, where the prevalence of psoriasis in adults varies from 0.44 to 2.8% [35].

Hence, we proposed to conduct an open label comparative interventional study of different clinically used doses rosuvastatin added to the standard first line drugs used in the treatment of psoriasis (topical beclomethasone, levocetirizine 5 mg and an olive oil blend emollient) to analyse its effects on PASI, DLQI, and MARS. For monitoring of the safety of the different rosuvastatin containing regimens used in the current study, periodic assessment of liver ALT and AST enzymes were also included.

The results of the present study can provide us valuable insights regarding the effectiveness of rosuvastatin on clinical improvement as well as quality of life in psoriasis; and may help in informed decision making about optimal use of rosuvastatin in such conditions.

Objectives:

The primary objective of this study was to evaluate the efficacy of the clinically used doses (5mg, 10 mg and 20 mg) of oral rosuvastatin in mild to moderate psoriasis based on PASI scores.

e-ISSN: 0975-1556, p-ISSN: 2820-2643

The secondary objectives were to assess quality of life based on DLQI, medication adherence based on MARS and safety based on hepatic ALT and AST levels with the different doses of oral rosuvastatin.

Materials and Methods

This was a prospective, open label, randomized controlled trial carried out in Dermatology OPD, Calcutta National Medical College & Hospital collaboration with Department of Pharmacology, CNMCH from the year 2021 to 2023. Sample size was calculated based on clinical cure (that is resolution of lesion with symptoms of erythema, thickness, and scaling) that was anticipated to be achievable at the end of 8 weeks of treatment, with an alpha of 0.05, and power of 80%. Based on that calculation and assuming a 20% anticipated dropout rate, a total of 52 subjects attending Dermatology outdoor diagnosed with mild to moderate plaque psoriasis were screened & enrolled as per selection criteria after fulfilling the inclusion & exclusion criteria, out of which total 48 patients completed the study.

Inclusion criteria consisted of adult patients with mild to moderate plaque psoriasis. On the other hand, patient allergic to rosuvastatin, patient with comorbidities like severe liver and kidney failure, history of recent operation, pregnant and lactating women and chronic alcoholics were excluded from the study.

Ethical considerations:

The study commenced only after approval from the Institutional Ethics Committee of Calcutta medical college and hospital, Kolkata prior to initiation of the study. Written informed consent was obtained from all subjects prior to screening and the study abided by the Declaration of Helsinki and the Indian Council of Medical Research ethical guidelines for biomedical research

with human subjects. The study was also registered at Clinical Trials Registry-India (CTRI) with registration no. REF/2022/03/052227.

Methodology

Selected study patients were randomized in outdoor dermatology following computer-generated randomization table into four groups with 13 study subjects each. All patients received the standard therapy of topical beclomethasone dipropionate cream 0.025% w/w twice daily, levocetirizine 5 mg once daily and an olive oil-based vitamin E emollient cream (Efatop PE) twice daily for the duration of therapy. In addition to standard therapy, patients in Group A, B and C received rosuvastatin in a dose of 5 mg, 10 mg, and 20 mg respectively. Group D was the control group and did not receive any dose of rosuvastatin apart from the standard treatment.

Individual patient details (age, sex, weight, BMI), history of cardiovascular diseases, smoking, medications obtained, family history, any side effects were noted in the Case Record Form. Other than screening cum baseline visit, patients were asked to report for 2 follow ups: 1st follow up at 4 weeks & 2nd follow up at 8 weeks.

At the baseline visit, each enrolled patient subjected to detailed clinical examination including routine laboratory blood tests and liver function tests including hepatic ALT and AST enzymes which were most pertinent to our study drug rosuvastatin. PASI score was recorded, and patients were requested to fill up both DLQI questionnaire. During each follow-up visit at the end of 4 weeks and 8 weeks, all the study measurements like PASI, DLQI, and liver enzyme levels were repeated. In addition, patients were provided the MARS questionnaire and the responses recorded during the follow up visits.

The psoriasis area and severity index (PASI) were used as the primary outcome measure in this study. It combines; and

percentage of body surface area affected in psoriasis. Body surface area is divided into four zones or sections with respective weightage for calculation of PASI: head (10%), arms (20%), trunk (30%) and legs (40%). For each individual section, the percentage of surface area affected by psoriasis is estimated and the severity of disease in terms of erythema, induration, and desquamation are assessed and scored separately. Then the sum of the three severity parameters is multiplied by the percentage of affected area for that zone and then multiplied finally by the respective weightage for that section. The composite scores for the 4 body sections thus obtained are combined to arrive at the final PASI score, and lower scores indicate better clinical outcome [27,28].

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As secondary outcome measures, we assessed the DLQI and MARS score. Dermatology Life Quality Index (DLQI) consists of 10 questions that investigates and rates patients' perception of how the disease has affected the different aspects of his/her quality of life over the last 7 days (e.g., Over the last week, how much has your skin influenced the clothes you wear/leisure or social activities etc). Here also lower scores indicate an improvement in quality of life [31].

Medication Adherence Rating Scale (MARS) is a self-reported questionnaire of 10 items with binary yes/no responses that seeks to measure the patient's compliance to the therapy (e.g., Do you ever forget to take your medication? or I take my medication only when I am sick etc.) Again, lower scores indicate better adherence [33].

Data management and statistical analysis

All the data were captured from source documents on a structured case report form (CRF). The data were first organized on a Microsoft Excel spreadsheet. GraphPad Prism version 9 software were then used for statistical analysis.

Routine descriptive statistics was used for summarization of data. For within group comparison of PASI, DLOI, AST, ALT against different time periods, repeated measures ANOVA with Tukey's multiple comparisons post hoc test was done. For between group comparison of these parameters at the same time interval we performed ordinary one-way ANOVA with Tukey's multiple comparison post hoc test. Similarly, for comparison of MARS between different group at a single time point, ordinary one-way ANOVA with Tukey's multiple comparison post hoc test was applied; while for comparing MARS scores at 4 weeks vs 8 weeks within the same group, paired t test was done. The p value of <0.05 was considered significant.

Results

Demographic details

Total 48 patients were included in this study. Among them there were 24 male and 24 female patients with a male to female ratio of 1:1. The mean age of the study population was 43.69 ± 10.72 years.

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Psoriasis Area and Severity Index Score

The PASI scores were compared within each study groups for intragroup changes in severity of psoriasis at baseline, and at the end of 4 weeks and 8 weeks. The same scores of each group were also compared against other groups to identify any intergroup differences in PASI at the same time periods (Figure 1).

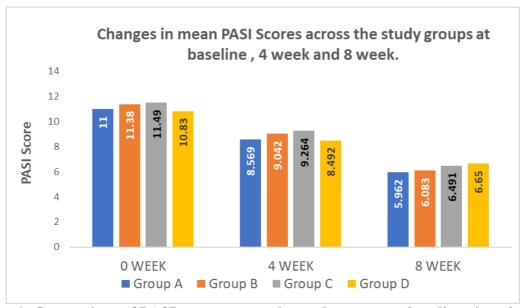


Figure 1: Comparison of PASI scores across the study groups at baseline, 4 week and 8 weeks. Test applied: Repeated measure ANOVA for intragroup analysis and one way ANOVA for intergroup analysis with Tukey's multiple comparison post hoc test.

Lower scores indicate better outcomes. At baseline, all the groups have comparable mean PASI scores (F=1.755, p=0.1697). There was highly significant reduction in the PASI scores in all the groups A (F=172.6, p=<0.0001), B (F=425.9, p=<0.0001), C (F=332.8, p=<0.0001) at the end of 4 weeks as well as 8 weeks compared to the baseline, including the control group i.e., group D (F=117.6, p=<0.0001),

implying a considerable reduction in severity of psoriasis across all groups.

However, comparison of PASI scores of the study groups against each other failed to show any significant differences either at the end of 4 weeks (F=1.030, p=0.3885) or 8 weeks (F=0.9542, p=0.4228), indicating the addition of rosuvastatin to standard therapy in psoriasis had minimal impact on PASI scores in this case.

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Dermatology Life Quality Index Questionnaire Score

Like the PASI scores, the DLQI scores were compared within groups as well as across the study groups at baseline, and at the end of 4 weeks and 8 weeks (Figure 2).

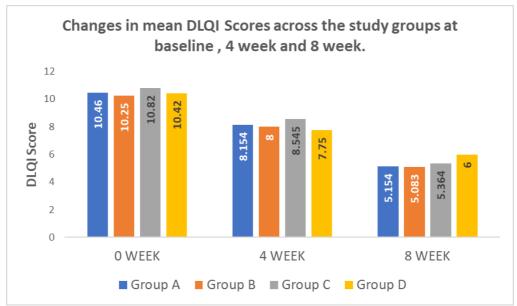


Figure 2: Comparison of DLQI scores across the study groups at baseline, 4 week and 8 weeks. Test applied: Repeated measure ANOVA for intragroup analysis and one way ANOVA for intergroup analysis with Tukey's multiple comparison post hoc test.

Lower scores indicate better outcomes All the groups had comparable DLQI scores at the baseline (F=1.779, p=0.1650); and similar to the PASI scores, there was significant improvement of DLQI scores within the groups A (F=240.7, p <0.0001), B (F=255.1, p<0.0001), C (F=340.6, p<0.0001) and D (F=179.4, p<0.0001) at 4 weeks as well as 8 weeks compared to the baseline. However, while comparing the DLQI scores of each group against one other, no meaningful differences were observed both at 4 weeks (F=1.710, p=0.1787) or 8 weeks (F=2.639, p=0.0613).

Once again it was noted that addition of rosuvastatin in any dose didn't contribute to any significant improvement of DLQI.

Medication Adherence Rating Scale (MARS)

The MARS Score was assessed at the end of 4 week and 8 weeks of therapy in all groups to evaluate attitudes about study medications and medication taking behaviour. On intragroup analysis a significant decrease in MARS score (p<0.0001) was observed in all the study groups from 4 weeks to 8 weeks (Figure 3).

Figure 3: Comparison of MARS scores across the study groups at 4 week and 8 weeks. Test applied: Paired t test for intragroup analysis and one way ANOVA for intergroup analysis with Tukey's multiple comparison post hoc test. Lower scores indicate better outcomes.

■ Group A Group B Group C Group D

Once again, when the MARS score of each group was compared against each other, no significant differences were observed at either 4 weeks (F=1.131, p=0.3470) or 8 weeks (F=1.947, p=0.1359), though the

net decrease in MARS values was smaller in group D compared to other groups.

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Liver enzymes

Hepatic ALT and AST levels were measured at baseline, 4 weeks, and 8 weeks for assessment of safety (Figure 4 and 5).

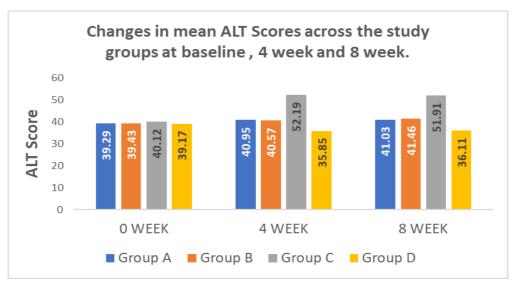


Figure 4: Comparison of ALT scores across the study groups at baseline, 4 week and 8 weeks. Test applied: Repeated measure ANOVA for intragroup analysis and one way ANOVA for intergroup analysis with Tukey's multiple comparison post hoc test.

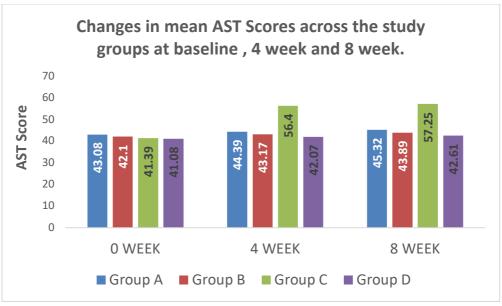


Figure 5: Comparison of AST scores across the study groups at baseline, 4 week and 8 weeks. Test applied: Repeated measure ANOVA for intragroup analysis and one way ANOVA for intergroup analysis with Tukey's multiple comparison post hoc test.

Comparing the ALT levels within each group, there was significant increase in ALT values in group A (F =15.02, p = 0.0002), B (F=23.21, p=0.0003) and C (F=98.71, p<0.0001) at 4 weeks and 8 weeks, though the ALT levels remained well within 3 times the normal value. Conversely, the ALT levels were significantly reduced in group D (F=4.559, p=0.0012) across the same time period.

Similar increase in the AST enzyme levels were noted in the groups A (F=22.40, p=0.0003), B (F=21.32, p=0.0002) and C (F=45.77, p<0.0001) at 4 weeks and 8 weeks. Interestingly in group D too, the AST levels were found to be increased (F=28.42, <0.0001) across the same time interval. However, like the ALT values, the changes in AST levels were also limited to less the 3 times the normal value and unlikely to be clinically significant. Group C which received the highest dose of study demonstrated the medication greatest excursions in both ALT and AST levels at both 4 weeks and 8 weeks, suggesting a possible dose dependent increase in liver enzymes with rosuvastatin therapy.

While comparing the liver enzyme levels of each group against one another, both ALT (F=0.07847, p=0.9713) and AST values (F=0.2275, p=0.8767) were comparable at the baseline. However, at the end of 4 weeks of treatment, Group C demonstrated significantly higher ALT p<0.0001) and AST (F=10.20, p<0.0001) values compared to other groups. Similar results were seen at the end of 8 weeks when the ALT (F=14.19, p<0.0001) and AST (F=11.00, p<0.0001) levels in Group C were again considerably higher than group A, B or D. As already mentioned, subjects in group C received highest dose of rosuvastatin and had largest increase in enzyme values among all the study groups, leading to these observations. However no other adverse effects of rosuvastatin like myopathy. renal dysfunction gastrointestinal or neurological problems were noted in any of the subjects throughout the study duration.

Discussion

There have been few RCTs and metanalysis that have investigated the use of different statins in the management of psoriatic disorders. In a systemic review conducted in 2017 by Ramessur and Gill noted that

there is insufficient evidence to support the use of oral statins as an adjunctive therapy to reduce the severity of psoriasis.[36]Another metanalysis by Socha et al. in 2019 [37], observed that while simvastatin led to significant improvements in PASI values, atorvastatin failed to provide any additional advantage when compared to placebo.

Rosuvastatin is a popular and established medication in treatment of dyslipidaemia. However, till date there are no notable RCT that have examined its effect on severity of psoriasis. Though the RORA-AS trial conducted in 2016 by Ikdahl et al. have generated some evidence to suggest that rosuvastatin may have anti-inflammatory properties and can improve endothelial function, it did not observe the effect of the drug on PASI or DLOI. Other limitations of the RORA-AS study include failure to analyse the subjects suffering from psoriasis as a separate group; and the fact that it was not a controlled trial. [26]

Another study conducted in 2018 by Sarian and Bolotna found that rosuvastatin 10 mg when combined with topical corticosteroids or phototherapy in moderate to severe psoriasis, led to significant decrease in PASI, inflammatory markers and VEGF levels. However, this again was not a RCT, and the effects of the drug on DLQI or MARS were not considered.[38]

In the present study highly significant reduction in the PASI scores were observed in all the groups including the control group at both the follow up visits. But on intergroup comparison, none of the groups receiving rosuvastatin demonstrated any advantages over the control group at any point of time in terms of improvement of PASI scores. Similar results were noted in case of DLQI, where while all the study groups had considerable improvement in the perceived quality of life scores at the end of both 4 and 8 weeks compared to the baseline; on comparison to the control arm none of the groups had any statistically

significant changes at point of the study duration. Again while comparing the MARS scores, we noted all the groups had a considerable improvement from 4 weeks to 8 weeks but none of them had any statistically significant advantage over the control group at either time intervals; though the magnitude of reduction in MARS score was less in the control group when compared against other treatment arms. All the study groups demonstrated an increase in AST scores across the study duration, but the largest change was noticed in group C where the patients received maximum doses of rosuvastatin i.e., 20 mg. The same group C also had the largest excursion in the ALT values, suggesting a possible dose dependant influence on the hepatic enzymes, though the levels were well within the 3 times of normal enzyme values and did not have any clinical significance in the present study. ALT values were also increased in the 5 mg and 10 mg rosuvastatin groups (Group A and B) but in the control group there was actually a reduction in ALT values by the end of study. From these observations we found no extra beneficial effect of addition of any dose of rosuvastatin to the standard therapy of topical beclomethasone, Levocetirizine and olive oil blend emollient in cases of plaque psoriasis. In fact, use of higher doses of rosuvastatin may be a potential concern of safety. Psoriasis is a complex condition with a wide range of severity and diverse clinical presentations. Every patient may respond differently to a given treatment due to factors such as genetic variations, coexisting medical conditions, concomitant medications, and lifestyle factors. It is possible that the therapeutic effect of rosuvastatin on psoriasis was simply insufficient to achieve a noticeable clinical advantage compared to the established treatments.

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While the observations of our study do not correspond to the results of few other small-scale studies [26,38] as mentioned above, our findings are consistent with the current

scientific consensus of available systemic reviews and metanalyses [36,37] that the evidence overall is not yet strong enough to make a definitive recommendation for the use of rosuvastatin in the treatment of plaque psoriasis.

There were some limitations of the present study that include inability to use placebo for control group; and the fact that it was not possible to implement blinding of the patients due to logistical constraints. While the effects of rosuvastatin evaluated in the study subjects for 8 weeks, further follow up of the patients were not continued so the long-term influence of the study medications were not accounted for.

Conclusion

While HMG CoA reductase inhibitors like rosuvastatin have garnered recent interest in management of psoriatic disorders due to anti-inflammatory and pleotropic actions, in the present study we could not identify any marked benefit of any dose of the drug when combined with topical glucocorticoids, antihistaminic and olive oil-based skin emollient combination. In addition, any potential benefits of statins for psoriasis would need to be weighed against their potential side effects and risks. This necessitates further research like large well designed RCTs to generate confirmatory evidence regarding the benefits and applicability of rosuvastatin as an adjuvant to established regimens in treatment of psoriasis.

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